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Strictly defined familial male breast cancer

Uwe Güth · Dieter Müller · Dorothy Jane Huang · Ellen Obermann · Hansjakob Müller

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Abstract The term "familial male breast cancer" is often misleading, because in the breast cancer families reported in the literature, the vast majority of the patients were women and only a few were men. In this report, we present the rare case of a strictly defined familial male breast cancer (MBC) in which exclusively men were diagnosed with breast cancer. Three of four brothers developed the disease between the age of 46 and 64 years within a period of 21 years whereas all female relatives remained unaffected. The three affected men did not show the typical known clinical and genetic risk factors for MBC. An X-linked recessive inheritance may be possible in these cases. One way to potentially improve the identification of the causes of MBC could be a through a strictly studying families in which the male members were exclusively diagnosed with this malignancy. This approach emphasizes familial MBC as a distinct entity and not only as a variant of female breast cancer.

U. Güth (✉) · D. J. Huang
Division of Gynecologic Oncology, Department of Gynecology and Obstetrics, University Hospital Basel (UHB), Spitalstrasse 21, 4031 Basel, Switzerland
e-mail: ugueth@uhbs.ch

D. Müller
Müller & Hess, Practice for Gynecology, Bahnhofstrasse 25, 4133 Pratteln, Switzerland

E. Obermann
Institute of Pathology, University of Basel, Schönbeinstrasse 40, 4031 Basel, Switzerland

H. Müller
Division of Medical Genetics (UKBB/DBM), University of Basel, Römergasse 5, 4005 Basel, Switzerland

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Introduction

Breast cancer in men is rare. The incidence is approximately 1% of that in women. Causes of male breast cancer are incompletely characterized and understood. Nevertheless, there is a definite association with family history and genetic factors [1–5]. In order to expose the influence of genetics on the disease, affected families were analyzed in detail and terms such as "male breast cancer families" [6–10] or "familial male breast cancer" [11–16] were introduced into the literature. These terms, however, are often misleading, because in the analyzed breast cancer families, the vast majority of the patients were women and only a few were men [11, 12, 14, 15]. We would prefer to narrow the definition of "familial male breast cancer" and use this term only for families in which exclusively *male* members are affected. In this report, we present the rare case of such a strictly defined "familial male breast cancer".

Case studies

We report the clinicopathologic, treatment and outcome characteristics of three brothers with familial breast cancer. These features, including the results of genetic testing of two of the men, are summarized in Table 1. Tumor stage was reported according to the current American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) TNM guidelines [17, 18]. Furthermore, we present on the basis of the pedigree important features of

Table 1 Summary of characteristics of three brothers with familial male breast cancer

	Case 1	Case 2	Case 3
Year of diagnosis	1982	1995	2003
Age at initial diagnosis	46	57	64
TNM classification (stage)[a]	pT1c pN1 cM0 (IIA)	pT1c pN0 cM0 (I)	pT1c pN0 cM0 (I)
Histological type	Ductal	Ductal	Ductal
Grading	G2	G2	G2
Hormone receptor-status	ER+ PR+	Unknown	ER+ PR−
HER-2/neu status	Negative	Unknown	Negative
Genetic findings			
BRCA1	Not done	Negative	Negative
BRCA2	Not done	Negative	Negative
TP53	Not done	Not done	Negative
Kind of surgery	BCT + ALD	Mastectomy + ALD	BCT + ALD
Adjuvant systemic treatment	No	No	No
Postoperative radiotherapy	Yes	No	Yes
Status	Dead (leukemia)	Alive, NED	Alive, NED
Age at the last follow-up, in living patients in July 2010	67	72	71
Breast cancer-specific survival (months)	250	185	81

ER Estrogen receptor, *PR* Progesterone receptor, *BCT* Breast-conserving therapy, *ALD* Axillary lymph node dissection

NED No evidence for disease

[a] AJCC (American Joint Committee on Cancer)/UICC (International Union Against Cancer) TNM Classification

the family history. All individuals tested for BRCA1/2 mutations gave signed informed consent.

Case 1

In 1982, at the age of 46, the oldest brother of the presented family was diagnosed with invasive ductal carcinoma in the central region of the right breast (stage IIA: pT1c pN1a [2/11] cM0; moderately differentiated grading [G2], hormonal receptor [HR] status: estrogen receptor [ER] positive, progesterone receptor [PR] positive, HER-2/neu negative). The patient's history was, with the exception of hepatitis B, unremarkable. The body mass index (BMI) was 28. He was surgically treated with breast-conserving therapy and axillary lymph node dissection. A standard adjuvant breast radiation was performed; systemic treatment was not recommended. In the subsequent years, with regard to breast cancer, he remained disease-free.

In 2002, the patient was diagnosed with acute myelogenic leukemia (AML) (French-American-British classification type M5a). With induction chemotherapy, a complete remission could be achieved. Prior to the intended allogeneic stem cell transplantation, however, he experienced a relapse. In 2003, 8 months after the initial diagnosis of AML, he died at the age of 67 of this disease. Survival time after initial diagnosis of breast cancer was 250 months.

Case 2

In 1995, at the age of 57, the second oldest brother of the family observed sanguineous discharge from the right nipple. Further diagnostic testing revealed a retromamillary lesion. After confirming a moderately differentiated invasive ductal carcinoma by core biopsy, the patient received a mastectomy and axillary lymph node dissection. According to the then valid guidelines for TNM stage I disease (pT1c pN0 [0/20] cM0; G2, ER/PR unknown, HER-2/neu unknown), he received neither postoperative radiotherapy nor adjuvant systemic treatment. The patient's preoperative history was unremarkable. The BMI was 27.

As of July 2010, at 185 months of follow up, the patient was still disease-free. No other malignancy has been found to this point.

Case 3

The third oldest brother of the family presented in 2003 at the age of 64 with a breast lump which was located in the left retromamillary region. Core biopsy revealed a moderately differentiated ductal invasive carcinoma and lumpectomy with axillary lymph node dissection was performed. For TNM stage I (pT1c pN0 [0/16] cM0; G2, ER positive, PR negative, HER-2/neu negative) disease, postoperative radiation was performed. The recommended

endocrine therapy with tamoxifen was declined by the patient. The preoperative history was unremarkable. The BMI was 25.

As of July 2010, at 81 months of follow up, the patient was still disease-free. No other malignancy has been found to this point.

Pedigree (Fig. 1)

The three male breast cancer patients have three other siblings. The youngest brother of the family remained up until now unaffected from breast cancer or other malignancies. In 2004, at the age of 64, a palpable lesion was surgically removed from the right breast; pathological examination showed a benign finding (dermoid cyst). Two sisters, today 67 and 68 years old, also remained unaffected from breast cancer at last contact. In the history of these three siblings, there were no hereditary or malignant diseases. The same holds true for the ancestry and the following generation. The father of the three men and a paternal uncle remained unaffected from breast cancer or other malignancies, like all the female family members (the mother of the brothers, and two aunts). For the deceased individuals, cardiovascular disease was the cause of the death.

Four siblings of the family (two of the breast cancer affected brothers, the unaffected brother and one sister) have all together 10 offspring. The medical histories of the nine females and one male individual are unremarkable to date.

Genetic testing

The BRCAPRO 5.0 model [19], which is considered to be a very useful tool for predicting BRCA1- and especially BRCA2-mutations in male breast cancer patients [20] calculated a mutation probability of 0.00 for the presence of a BRCA1-, but one of 0.982 for that of a BRCA2 mutation. However, no mutation in both genes could by identified by two independent laboratories. The exons of the BRCA1- and BRCA2-gene and the neighbouring sequences of the introns were analyzed after PCR amplification. In addition, a MLPA—(Multiplex Ligation-dependent Probe Amplification) analysis has been used (SALSA MLPA kits BRCA1 P002-C1 and BRCA2 P090-A2; MCR Holland). A germline TP53-mutation was also excluded in case 3 by sequencing its exons.

Discussion

In this report, we present the rare case of a strictly defined "familial male breast cancer" in which exclusively men were diagnosed with breast cancer. Three of four brothers developed the disease between the age of 46 and 64 years within a period of 21 years whereas all female relatives remained unaffected. Remarkably, the three affected men did not show the typical known clinical and genetic risk factors for MBC. Two of these men have children.

Both genetic and lifestyle/environmental factors have been implicated in the etiology of breast cancer, which is a

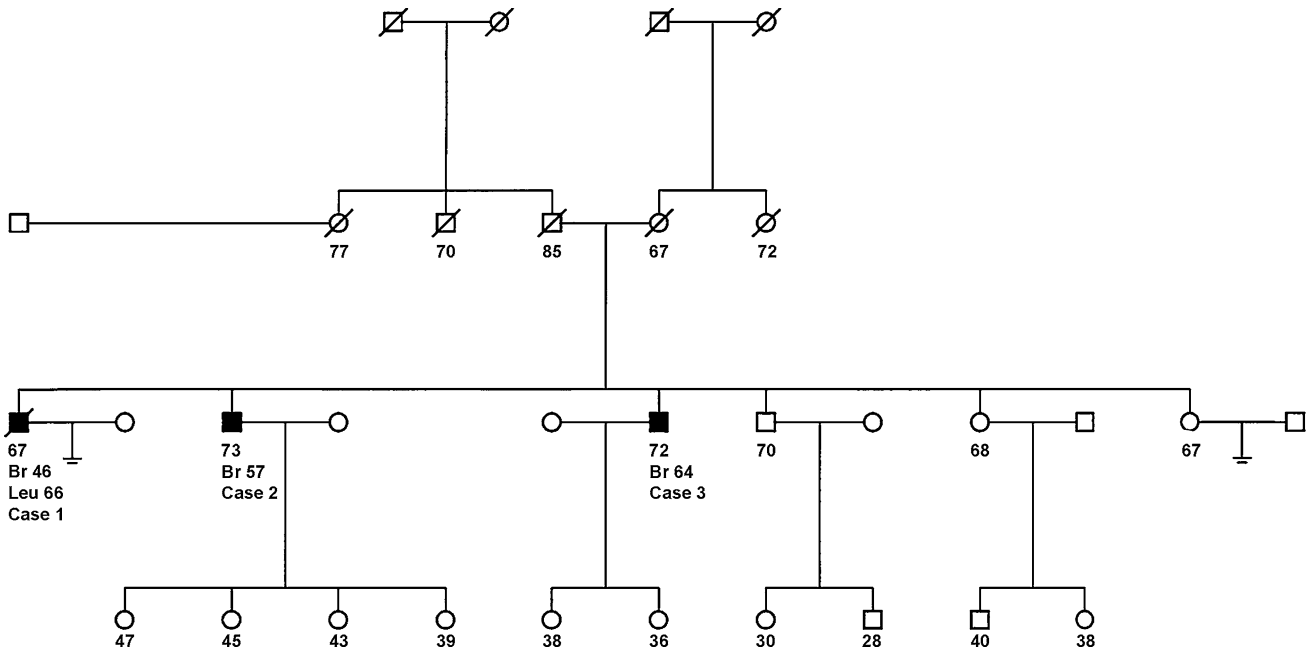

Fig. 1 Family pedigree. *Br* Breast cancer, *Leu* Leukemia, *First number* Current age or age at death, *Second number* Age at breast cancer diagnosis

heterogeneous disease. As with cancer of the female breast, the causes of male breast cancer (MBC) are incompletely characterized and understood. Nevertheless, there is a definite association with family history and genetic factors [1–5]. Approximately 15% to 20% of men with breast cancer report a family history of breast or ovarian cancer [3]. Only a few genes having high penetrance mutations have been shown to be involved in the etiology of MBC. BRCA2 is the most clearly associated gene mutation [1–3]; in some families with BRCA2-mutations, multiple affected male relatives had been observed [6]. In the reported family, however, a mutation of this gene could not be found. Further associations have been suggested for BRCA1, PTEN, P53, and CHEK2 [1–3]. The presence of other high penetrance germ line mutations of other genes suggested were to be involved in the pathogenesis of MBC, such as BRCA1 and TP53 mutations found in the Li-Fraumeni cancer syndrome, as well as PTEN mutations typical for the Cowden syndrome or STK11/LKB1 mutations as observed in the Peutz-Jeghers syndrome could be excluded by genetic analysis (BRCA1 and TP53) or on grounds of clinical and familial features. No MBC was observed in the families with pathogenic mutations of the RAD51C gene [21]. The CHEK2 1100delC variant, not analyzed in this study, is unlikely to account for a significant fraction of MBC [22–25]. PALB2 was found to be a breast cancer predisposition gene [26]. Several pedigrees reported in the literature to carry protein-truncating PALB2 mutations also contained MBC patients. The study of Sauty de Chalon et al., which included 25 MBC cases of such families, however, provided no evidence that germline PALB2 mutations are associated with an increased risk of MBC [27].

The fact that only males are affected in a family is typical for X-linked recessive inheritance even if some women occasionally manifest features of an X-linked recessive trait. No high or moderate- to low penetrance gene associated only with breast cancer, however, have been identified on the X-chromosome so far [28].

Hormonal levels, particularly increased circulating estradiol levels and disturbed estrogen/testosterone ratio, may contribute to an increased risk of the disease [1–3]. Increased estradiol levels might be caused by factors such as cirrhosis of the liver, obesity and exogenous estrogen. Furthermore, testicular abnormalities such as undescended testes, congenital inguinal hernia, orchiectomy, orchitis, and infertility were reported to be risk factors for MBC [1–3]. None of our three MBC patients had the above mentioned conditions or testicular problems, and all except one of the brothers of the family had children. Furthermore, recognized risk factors such as Klinefelter's syndrome or androgen hyposensitivity (Reifenstein's syndrome) can be clearly excluded in the presented family, due to a lack of the distinct and clinically easily recognizable features which are associated with these disorders. It has been reported that working in hot environments might enhance the risk for male breast cancer, possibly because long-lasting exposure to high ambient temperature can lead to testicular failure [1]. One of the three brothers (case 2) worked for many years with furnaces in the ceramic industry.

Several authors evaluated oncogenic influences on the breast during fetal life and infancy [29, 30]. In our reported cases, it is notable that the three breast cancer affected brothers were born before World War II (born in 1936, 1937 and 1938); the three unaffected siblings, however, were born during the war (born in 1940, 1943 and 1944). It is certain that the older brothers were exposed to different nutritional situations both in utero and in early infancy compared to the three siblings who were born in an environment of war-time insufficiencies. These influences cannot be completely retrospectively confirmed today; a gene-environment interaction, however, may be hypothesized.

The available data on MBC arise from small studies involving few patients often belonging to a small geographic area. Larger MBC cohorts should therefore be collected for candidate gene, genome-wide association studies (GWAS) or for the analysis of gene-environment interactions. One way to potentially improve the identification of the causes of MBC could be a through a strictly studying families in which the male members were exclusively diagnosed with this malignancy. This approach emphasizes familial MBC as a distinct entity [2, 3] and not only as a variant of female breast cancer.

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